

SAFETY DATA SHEET

Prepared to U.S. OSHA, CMA, ANSI, Canadian WHMIS Standards, European Union CLP EC 1272/2008 and the Global Harmonization Standard

PART I *What is the material and what do I need to know in an emergency?*

1. PRODUCT IDENTIFICATION

IDENTIFICATION of the SUBSTANCE or PREPARATION:

TRADE NAME (AS LABELED): FLUDARABINE PHOSPHATE INJECTION
CHEMICAL NAME: Active Ingredient: 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)
CHEMICAL CLASS: Active Ingredient: Purine Nucleoside Cytotoxic Agent
PRODUCT USE: Human Pharmaceutical

COMPANY/UNDERTAKING IDENTIFICATION:

U.S. SUPPLIER/MANUFACTURER'S NAME: TEVA
ADDRESS: 1090 Horsham Road
 North Wales, PA 19454
 215-591-3000 [08:00 AM --> 05:00 PM]
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EUROPEAN SUPPLIER/MANUFACTURER'S NAME: TEVA/TAPI
ADDRESS: Sicom sri-Via Terrazzano
 77-20017 Cho (MI), Italy
 +39 02 93197 306 [08:00 AM --> 05:00 PM]
BUSINESS PHONE:

EMERGENCY PHONE: United States/Canada/Puerto Rico: 1-800/424-9300 (Chemtrec) [24-hrs]
 International: 01-703-527-3887 (Chemtrec) [24-hours]

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DATE OF REVISION: New

ALL WHMIS required information is included in appropriate sections based on the ANSI Z400.1-2004 format. This product has been classified in accordance with the hazard criteria of the CPR and the SDS contains all the information required by the CPR. The product is also classified per all applicable EU Directives through EC 1907: 2006, the European Union CLP EC 1272/2008 and the Global Harmonization Standard.

2. HAZARD IDENTIFICATION

GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU LABELING/CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

EMERGENCY OVERVIEW: Product Description: This product is clear, colorless, odorless liquid. **Health Hazards:** WARNING! THIS PRODUCT CONTAINS A POWERFUL CYTOTOXIC AGENT. EXPOSURE BY ALL ROUTES OF EXPOSURE MUST BE AVOIDED. Toxic by injection. May be harmful or fatal by inhalation and ingestion. May be harmful by skin contact. Therapeutic use can cause compromise of the immune system, cause depression of bone marrow, pulmonary toxicity, neurological toxicity, adverse central nervous system effects, rash, fever and eye infections, gastrointestinal, hematological, and hepatic effects and occasionally, cardiovascular effects. Fludarabine is a suspect mutagen and reproductive toxin, based on animal testing. May cause harm or be fatal to developing fetus. **Flammability Hazards:** This solution is not flammable or combustible. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon and nitrogen oxides). **Reactivity Hazards:** This product is not reactive. **Environmental Hazards:** This product has not been tested for environmental harm; all release to the environment should be avoided. **Emergency Recommendations:** Emergency responders must wear personal protective equipment suitable for the situation to which they are responding.

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/w	EU Classification (67/548/EEC) GHS & EU Classification (1272/2008 EC) Risk Phrases/Hazard Statement Codes
Fludarabine Phosphate	75607-67-9	For Freebase, CAS# 21679-14-1; 244-525-5	proprietary	SELF CLASSIFICATION: EU 67/548 Classification: Harmful, Reproductive Toxicity Cat. 3, Germ Cell Mutagenicity Cat. 3, Risk Phrases: R20/21/22, R62/63, R68 Symbols: Xn GHS & EU 1272/2008 Classification: Acute Oral Toxicity Cat. 5, Acute Dermal Toxicity Cat. 5, Acute Inhalation Toxicity Cat. 5, STOT (Injection-Blood Forming, Immune, Neurological, Central and Peripheral Nervous Systems) RE Cat. 1, Germ Cell Mutagenicity Cat. 2, Reproductive Toxicity Cat. 2 Hazard Statement Codes: H303 + H313 + H333, H341, H361fd, H372 Hazard Symbols/Pictograms: GHS07, GHS08
EXCIPIENTS				
D-Mannitol	69-65-8	200-711-8	proprietary	EU 67/548 Hazard Classification: Not Applicable GHS & EU 1272/2008 HAZARD CLASSIFICATION: Not Applicable
Water for Injection	7732-18-5	231-791-2	Balance	EU 67/548 Hazard Classification: Not Applicable GHS & EU 1272/2008 Hazard Classification: Not Applicable

NOTE: This product contains a trace amount of Sodium Hydroxide for pH adjustment only. No classification is given. See Section 16 for full classification information of product and components.

PART II *What should I do if a hazardous situation occurs?*

4. FIRST-AID MEASURES

DESCRIPTION OF FIRST AID MEASURES: Contaminated individuals must be taken for medical attention if any adverse effects occur. Remove contaminated clothing and shoes. Wash clothing and thoroughly clean shoes before reuse. Take a copy of label and SDS to health professional with victim.

SKIN EXPOSURE: If this product contaminates the skin, begin decontamination with running water. Minimum flushing is for 20 minutes. The contaminated individual must seek medical attention if any adverse effects occur after flushing.

EYE EXPOSURE: If this product enters the eyes, open contaminated individual's eyes while under gently running water. Use sufficient force to open eyelids. Have contaminated individual "roll" eyes. Minimum flushing is for 20 minutes. Contaminated individual must seek medical attention if adverse effect continues after flushing.

INHALATION: If this product is inhaled, remove victim to fresh air. The contaminated individual must seek medical attention if any adverse effects occur.

INGESTION: If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, do not induce vomiting. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow. If victim is convulsing, maintain an open airway and obtain immediate medical attention.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Respiratory, skin, gastrointestinal, hepatic, blood forming and nervous, neurological, liver, renal and hepatic disorders may be aggravated by exposure to this product. In addition, existing disorders to the target organs, described in Section 11, may also be aggravated by exposure to this product.

INDICATION OF IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT IF NEEDED: Treat symptoms and eliminate overexposure. Treat symptoms and eliminate overexposure. There is no specific antidote for this drug. Effective countermeasures aimed at controlling hematologic side effects may include bone marrow transplantation and transfusions (platelets, blood) or the administration of hematologic growth factors. Supportive therapy should be fully used. It is not known whether this product or its metabolites can be removed by dialysis. No relevant experience is available.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not applicable.

AUTOIGNITION TEMPERATURE: Not applicable.

FLAMMABLE LIMITS (in air by volume, %): Not applicable.

FIRE EXTINGUISHING MEDIA: Unless incompatibilities exist for surrounding materials, carbon dioxide, water spray, 'ABC' type chemical extinguishers, foam, dry chemical and halon extinguishers can be used to fight fires involving this product.

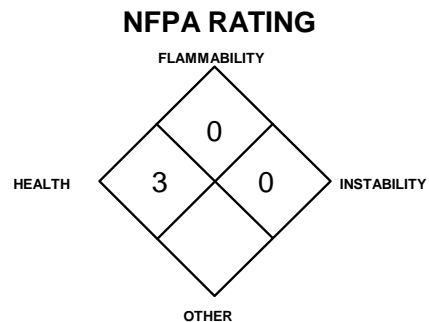
UNSUITABLE FIRE EXTINGUISHING MEDIA: None known.

SPECIAL HAZARDS ARISING FROM THE SUBSTANCE: This product is not flammable. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon and nitrogen oxides).

Explosion Sensitivity to Mechanical Impact: Not sensitive.

Explosion Sensitivity to Static Discharge: Not sensitive.

ADVICE TO FIRE-FIGHTERS: Structural firefighters must wear Self-Contained Breathing Apparatus and full protective equipment. All personal protective gear and contaminated fire-response equipment should be decontaminated with soapy water before being returned to service. Move fire-exposed containers if it can be done without risk to firefighters. If possible, prevent runoff water from entering storm drains, bodies of water, or other environmentally sensitive areas.



Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate
3 = Serious 4 = Severe

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES: Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. It is suggested that kits include a respirator, chemical splash goggles, two pairs of gloves, two sheets (12 x 12) of absorbent material, 250-mL and 1-liter spill control pillows and a small scoop to collect glass fragments (if applicable). Absorbents should be incinerable. Finally, the kit should contain two large waste-disposal bags. Avoid aerosols of this product during spill response procedures. Decontaminate the area of the spill thoroughly by using a bleach solution and a detergent solution followed by clean water. The proper personal equipment for incidental releases should include gloves, safety glasses, and a lab coat. All contaminated material should be labeled as cytotoxic waste.

PROTECTIVE EQUIPMENT:

Small Spills/Spills in Hoods: Personnel wearing gowns, double nitrile or latex gloves and eye protection should immediately clean spills of less than 5 mL outside a hood.

Large Spills: Use proper protective equipment, including double nitrile or latex gloves, full body gown, and full-face respirator equipped with with an organic mist filter. Self-Contained Breathing Apparatus (SCBA) can be used instead of an air-purifying respirator.

METHODS FOR CLEAN-UP AND CONTAINMENT:

Cleanup of Small Spills: Liquids should be wiped with absorbent gauze pads; solids should be wiped with wet absorbent gauze. Clean the spill area (three times) using a bleach solution and detergent solution and then rinse with clean water.

Spills in Hoods: Decontamination of all interior hood surfaces may be required after the above procedures have been followed.

6. ACCIDENTAL RELEASE MEASURES (Continued)

METHODS FOR CLEAN-UP AND CONTAINMENT (continued):

Spills in Hoods (continued): If the HEPA filter of a hood is contaminated, label the unit "Do not use-contaminated" and have trained personnel wearing appropriate protective equipment change and dispose of the filter properly as soon as possible.

Large Spills: Review Sections 2, 8, 11 & 12 before proceeding with cleanup. For spills of amounts larger than 5 mL or 5 g limit spread by gently covering with absorbent sheets or spill-control pads or pillows or, if a powder is involved, cover with damp cloths or towels. Be sure not to generate aerosols. Restrict access to the spill areas. The dispersion of mists or sprays into surrounding air and the possibility of inhalation is a serious matter and should be treated as such. Do not apply chemical in-activators as they may produce hazardous by-products. Thoroughly clean all contaminated surfaces three times and rinse with clean water OR use bleach solution to expedite degradation of this product into less hazardous materials, wash with a detergent solution, and rinse with clean water.

All Spills: Place all spill residues in an appropriate, labeled container and seal. Move to a secure area. Dispose of in accordance with Federal, State, and local hazardous waste disposal regulations (see Section 13, Disposal Considerations). For spills on water, contain, minimize dispersion and collect. Dispose of recovered material and report spill per regulatory requirements.

ENVIRONMENTAL PRECAUTIONS: Prevent material from entering sewer or confined spaces, waterways, soil or public waters. Do not flush to sewer. For spills on water, contain, minimize dispersion and collect.

REFERENCE TO OTHER SECTIONS: Review Sections 2, 8, 11 and 12 before proceeding with cleanup. See Section 13, Disposal Considerations for more information.

PART III *How can I prevent hazardous situations from occurring?*

7. HANDLING and STORAGE

NOTE: Consistent with the OSHA Bloodborne Pathogen regulation (29 CFR 1910.1030), observe Universal Precautions while using this product. Place used or product-contaminated hypodermic needles and syringes in a rigid "Sharps" container. Do not recap or clip used or product-contaminated hypodermic needles.

PRECAUTIONS FOR SAFE HANDLING: THIS PRODUCT CONTAINS A POWERFUL CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL. All employees who handle this material should be thoroughly trained to handle it safely. Special attention must be paid in avoiding releasing airborne particles of this material in areas in which this compound is handled or used. As with all chemicals, avoid getting this product ON YOU or IN YOU. Do not eat, smoke or drink while handling this material. Smokers who do not take simple protective measures such as gloving and hand washing may take in additional amounts of the drug orally through contaminated cigarettes, resulting in exposure. Appropriate personal protective equipment must be worn (see Section 8, Engineering Controls and Personal Protection). Avoid generation of aerosols. Areas in which this product is used should be wiped down, so that this product does not accumulate. Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this product, and during patient administration. Operations of high risk associated with the use of this product include:

- Withdrawal of needles from drug vials;
- Drug transfers using syringes and needles or filter straws;
- Opening ampoules; and
- Expulsion of air from drug-filled syringes.

DO NOT CLIP OR CRUSH NEEDLE WITH WHICH THIS PRODUCT WAS IN CONTACT. Use of this product should meet the following provisions:

- Work should be performed in a designated area for working with hazardous drugs;
- Containment devices, such as a Biological Safety Cabinet, should be used;
- Contaminated waste must be properly handled; and
- Work areas must be regularly decontaminated.

CONDITIONS FOR SAFE STORAGE: Have appropriate extinguishing equipment in the storage area (e.g., sprinkler system, portable fire extinguishers). Recommended Storage Temperature: 2-8°C (35-46°F). Store containers in a cool, dry location, away from direct sunlight and sources of intense heat. Store away from incompatible materials (see Section 10, Stability and Reactivity). Material should be stored in secondary containers. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged. Empty containers may contain residual product; therefore, empty containers should be handled with care

SPECIFIC END USE(S): This product is a human pharmaceutical. Follow all industry standards for handling of pharmaceutical materials.

PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT: When cleaning non-disposable equipment, wear latex or nitrile gloves (double gloving is recommended), goggles, and lab coat. Wash equipment with soap and water or autoclave as appropriate. Dispose of all needles, syringes, vials, and other contaminated disposable items properly.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

VENTILATION AND ENGINEERING CONTROLS: Use with adequate ventilation. Follow standard medical product handling procedures. Admixtures or manipulations of this drug should be carried out in a cytotoxic drug safety cabinet. The cabinet should be regularly cleaned following the manufacturer's recommendations, but no less frequently than weekly. All surfaces should be thoroughly washed with water and detergent and triple rinsed. During decontamination, workers should wear the same equipment recommended in Section 6 (Accidental Release Measures) of this SDS for the clean up of a large spill.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION (Continued)

EXPOSURE LIMITS/CONTROL PARAMETERS (continued):

VENTILATION AND ENGINEERING CONTROLS (continued): HEPA filters on the cytotoxic drug safety cabinet should be changed every six months. The safety cabinet should be tested and certified as recommended by the National Sanitation Foundation in Standard Number 49. Ensure eyewash stations are available and accessible in areas where this product is used. Wipe down work areas routinely to prevent accumulation of product.

WORKPLACE EXPOSURE LIMITS/CONTROL PARAMETERS:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELS		NIOSH	OTHER
		TWA mg/m ³	STEL mg/m ³	TWA mg/m ³	STEL mg/m ³	TWA mg/m ³	STEL mg/m ³	IDLH mg/m ³	mg/m ³
Fludarabine Phosphate	75607-67-9	NE	NE	NE	NE	NE	NE	NE	NE
Mannitol	69-65-8	NE	NE	NE	NE	NE	NE	NE	NE

NE = Not Established

See Section 16 for Definitions of Other Terms Used

INTERNATIONAL OCCUPATIONAL EXPOSURE LIMITS: Currently, there are no international limits established for the components of this product. Limits change or are added and should be checked for currency.

PROTECTIVE EQUIPMENT: *The following information on appropriate Personal Protective Equipment is provided to assist employers in complying with OSHA regulations found in 29 CFR Subpart I (beginning at 1910.132, including U.S. Federal OSHA Respiratory Protection (29 CFR 1910.134), OSHA Eye Protection 29 CFR 1910.133, OSHA Hand Protection 29 CFR 1910.138, OSHA Foot Protection 29 CFR 1910.136 and OSHA Body Protection 29 CFR 1910.132), equivalent standards of Canada (including CSA Respiratory Standard Z94.4-02, Z94.3-M1982, Industrial Eye and Face Protectors and CSA Standard Z195-02, Protective Footwear), or standards of EU member states (including EN 529:2005 for respiratory PPE, CEN/TR 15419:2006 for hand protection, and CR 13464:1999 for face/eye protection). Please reference applicable regulations and standards for relevant details.*

RESPIRATORY PROTECTION: Maintain airborne contaminant concentrations below exposure limits listed above if applicable. If necessary, use only respiratory protection authorized under appropriate regulations. Oxygen levels below 19.5% are considered IDLH by U.S. OSHA. In such atmospheres, use of a full-facepiece pressure/demand SCBA or a full facepiece, supplied air respirator with auxiliary self-contained air supply is required under U.S. OSHA's Respiratory Protection Standard (1910.134-1998).

EYE PROTECTION: No eye protection is normally needed during medical administration of this product. During operations in which mists or sprays of the product may be generated, splash goggles or safety glasses should be considered. If necessary, refer to appropriate regulations.

HAND PROTECTION: During medical administration of this product, medical latex or nitrile gloves should be worn to avoid absorption of the active ingredient. Check gloves for leaks. Wash hands before putting on gloves and after removing gloves. During manufacture or other similar industrial operations, wear neoprene rubber gloves. Use triple gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS. If necessary, as described in appropriate regulations.

SKIN PROTECTION: Use appropriate protective clothing for the task (e.g., lab coat, etc.). If necessary, refer to the U.S. OSHA Technical Manual (Section VII: Personal Protective Equipment) or other appropriate regulations.

9. PHYSICAL and CHEMICAL PROPERTIES

FORM: Liquid.

ODOR: Odorless.

MOLECULAR FORMULA: For active: C₁₀H₁₃FN₅O₇P

RELATIVE VAPOR DENSITY (air = 1): Not available.

SPECIFIC GRAVITY (water = 1): Not available.

VAPOR PRESSURE, mm Hg @ 20°C: Not available.

OXIDIZING PROPERTIES: Not an oxidizer.

SOLUBILITY IN WATER: Soluble

COEFFICIENT OF OIL/WATER DISTRIBUTION (PARTITION COEFFICIENT): Not available.

HOW TO DETECT THIS SUBSTANCE (identification properties): There are no good warning properties to identify it in event of an accidental release.

COLOR: Clear, colorless.

ODOR THRESHOLD: Not applicable.

FREEZING POINT: ~0°C (~212°F)

EVAPORATION RATE (n-BuAc = 1): Not available.

BOILING POINT: ~100°C (~212°F)

pH: Not available.

EXPLOSIVE PROPERTIES: Not applicable.

OTHER SOLUBILITY: Not available.

10. STABILITY and REACTIVITY

REACTIVITY/CHEMICAL STABILITY: Not reactive. Stable under normal conditions.

DECOMPOSITION PRODUCTS: *Combustion:* Carbon and nitrogen oxides. *Hydrolysis:* None known.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: Strong acids and other material incompatible with typical medical preparations and materials that are incompatible with water.

POSSIBILITY OF HAZARDOUS POLYMERIZATION: Will not occur.

CONDITIONS TO AVOID: Exposure to or contact with extreme temperatures, incompatible chemicals.

PART IV *Is there any other useful information about this material?*

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF OVEREXPOSURE BY ROUTE OF EXPOSURE: The main routes of occupational overexposure to this product are via contact with skin or eyes. Although toxicity of this product is mainly by injection, as it contains a cytotoxic compound, all exposure must be minimized. May also be toxic by inhalation, skin contact and ingestion.

11. TOXICOLOGICAL INFORMATION (Continued)

INHALATION: Inhalation of the product is not anticipated to be a likely form of exposure to this product. If inhaled, irritation of the nose and upper respiratory system may occur. Symptoms of such overexposure may include irritation of respiratory system. Other symptoms as described under 'Health Effects from Therapeutic Use' may occur.

CONTACT WITH SKIN or EYES: Contact may cause mild irritation. Effects may include stinging, watering, and redness of the eyes and redness and a burning sensation of the skin. May be cause systemic toxicity in contact with skin with symptoms as described under 'Health Effects from Therapeutic Use'.

SKIN ABSORPTION: This product may be absorbed via skin and cause adverse effects as described under 'Health Effects from Therapeutic Use'.

INGESTION: Ingestion of this product is not anticipated to be a significant route of occupational overexposure. Ingestion of this product (i.e., through poor hygiene practices) may cause irritation of the gastrointestinal system and may also cause adverse effects as described under 'Health Effects from Therapeutic Use'.

INJECTION: This product is toxic by injection. Local redness and pain are the primary symptoms of accidental injection in an occupational setting. Medical personnel are not anticipated to experience over-exposures to the therapeutic doses of this product. However, effects including bone marrow suppression with decreased blood cells, nausea, vomiting, severe gastrointestinal distress, loss of blood pressure, cardiac irregularities and hair loss may occur. Other symptoms described under 'Health Effects from Therapeutic Use'.

HEALTH EFFECTS FROM THERAPEUTIC USE: This product is administered by intravenous infusion injection. The most common acute toxicity effects include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Later effects include bone marrow depression, compromise of immune system, central nervous and peripheral nervous system effects (weakness, agitation, confusion), neurological toxicity, visual disturbances, renal damage (with higher doses), pulmonary infiltrates and toxicity, and tumor lysis syndrome. The bone marrow depressant effects of Fludarabine Phosphate may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. Fludarabine Phosphate is associated with severe neurotoxicity at high doses, with effects including altered mental status, photophobia, amaurosis (blindness that usually is temporary without change in the eye itself), generalized seizures, spastic or flaccid paralysis, quadriparesis and coma, which can progress to death despite discontinuation of therapy in some instances. In men, this drug has caused testicular dysfunction. Therapeutic use can cause potentially life-threatening autoimmune hemolytic anemia.

Tumor lysis syndrome has been reported. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

HEALTH EFFECTS OR RISKS FROM EXPOSURE (An explanation in lay terms).

ACUTE: This product is toxic by all routes of exposure. Immediate acute effects are nausea and vomiting.

CHRONIC: Chronic exposure to this product in therapeutic use can cause toxic effects to the cardiovascular system, gastrointestinal system, neurological, central and peripheral nervous systems. The active ingredient is a suspect reproductive toxin, mutagen and carcinogen.

TARGET ORGANS: *Acute: Occupational Exposure:* Skin, eyes, respiratory system. *Therapeutic Use:* Skin, gastrointestinal system. *Chronic: Occupational Exposure:* Not known. *Therapeutic Use:* Skin, immune system, reproductive system, blood producing system, neurological system, central and peripheral nervous systems.

TOXICITY DATA: The following data are available for the active ingredient of this product. Toxicity data are available for the excipient ingredients, but are not presented in this SDS. Contact Teva for additional information.

FLUDARABINE PHOSPHATE:

TDLo (Intravenous-Child) 18,750 mg/kg/5 days-intermittent: Brain and Coverings: encephalitis; Sense Organs and Special Senses (Eye): visual field changes

TDLo (Intravenous-Human) 4,380 mg/kg/168 days-intermittent: Blood: lymphoma, including Hodgkin's disease; Tumorigenic: protects against induction of experimental tumors, active as anti-cancer agent

TDLo (Intravenous-Man) 17,760 mg/kg/5 days-intermittent: Brain and Coverings: demyelination; Behavioral: hallucinations, distorted perceptions; Behavioral: coma

FLUDARABINE PHOSPHATE (continued):

TDLo (Intravenous-Man) 11,655 mg/kg/5 days-intermittent: Sense Organs and Special Senses (Eye): visual field changes, ptosis; Behavioral: somnolence (general depressed activity)

TDLo (Intravenous-Woman) 14,245 mg/kg/5 days: Sense Organs and Special Senses (Eye): effect, not otherwise specified; Behavioral: excitement; Skin and Appendages: sweating

TDLo (Intravenous-Woman) 23,125 mg/kg/5 days-intermittent: Brain and Coverings: encephalitis; Sense Organs and Special Senses (Eye): visual field changes; Behavioral: somnolence (general depressed activity)

FLUDARABINE PHOSPHATE (continued):

LD₅₀ (Intravenous-Mouse) 1236 mg/kg: Behavioral: somnolence (general depressed activity)

LD₅₀ (Intravenous-Rat [male]) 910 mg/kg

LD₅₀ (Intravenous-Rat [female]) 1050 mg/kg

LD₅₀ (Intravenous-Mouse [male]) 1404 mg/kg

LD₅₀ (Intravenous-Mouse [male]) 593 mg/kg/5 days



LD₅₀ (Intravenous-Mouse [female]) 1235 mg/kg

LD₅₀ (Intravenous-Mouse [male/female]) 1321 mg/kg

LD₅₀ (Intravenous-Mouse [female]) 496 mg/kg/5 days

Cytogenetic Analysis (Human Lymphocyte) 1 mg/L/72 hours-continuous

CARCINOGENIC POTENTIAL OF COMPONENTS: No animal carcinogenicity studies with Fludarabine Phosphate have been located.

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM			
HEALTH HAZARD	(BLUE)	3*	
FLAMMABILITY HAZARD	(RED)	0	
PHYSICAL HAZARD	(YELLOW)	0	
PROTECTIVE EQUIPMENT			
EYES	RESPIRATORY	HANDS	BODY
	SEE SECTION 8		SEE SECTION 8
For Routine Industrial Use and Handling Applications			

Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate
3 = Serious 4 = Severe * = Chronic hazard

11. TOXICOLOGICAL INFORMATION (Continued)

CARCINOGENIC POTENTIAL OF COMPONENTS (continued): The remaining components of this product are not found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH and therefore are neither considered to be nor suspected to be cancer-causing agents by these agencies.

IRRITANCY OF PRODUCT: It is anticipated that this product may irritate the respiratory system, mucous membranes, skin, and eyes.

SENSITIZATION TO THE PRODUCT: This product is not known to cause human skin or respiratory sensitization.

REPRODUCTIVE TOXICITY INFORMATION: This product is rated Pregnancy Category D (POSITIVE EVIDENCE OR RISK, There is a risk to fetus after drug is administered, but under certain circumstances [e.g., treatment of life-threatening illnesses], the benefits can outweigh the risk). The following information is available for the active component of this product.

Mutagenicity: Fludarabine Phosphate was clastogenic *in vitro* to Chinese hamster ovary cells (chromosome aberration assay) in the presence of metabolic activation and induced sister chromatid exchanges both in the presence and absence of metabolic activation. In addition, Fludarabine Phosphate was clastogenic *in vivo* (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in male mice). Fludarabine Phosphate was not mutagenic to bacteria (Ames test) or mammalian cells either in the presence or absence of metabolic activation.

Embryotoxicity: Fludarabine Phosphate was embryo-lethal in both rats and rabbits. In rats, repeated intravenous doses of Fludarabine Phosphate at 1.5 times and 4.5 times the recommended human oral dose (40 mg/m²) administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (cleft palate, exencephaly, and fetal vertebrae deformities) and decreased fetal body weights. Maternal toxicity was not apparent at 1.5 times the human oral dose, and was limited to slight body weight decreases at 4.5 times the human oral dose. In rabbits, repeated intravenous doses of Fludarabine Phosphate at 2.4 times the human oral dose administered during organogenesis increased embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses.

Teratogenicity: Fludarabine Phosphate was teratogenic in both rats and rabbits. A significant increase in malformations including cleft palate, hydrocephaly, adactyly, brachydactyly, fusions of the digits, diaphragmatic hernia, heart/great vessel defects, and vertebrae/rib anomalies were seen in all dose levels (≥ 0.3 times the human oral dose).

Reproductive Toxicity: Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. Many drugs can be present in breast milk, causing adverse effects to breast-fed babies. This drug should not be used by pregnant or nursing women.

BIOLOGICAL EXPOSURE INDICES: Currently, there are no Biological Exposure Indices (BEIs) determined the components of this product.

12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

MOBILITY IN SOIL: This product has not been tested for mobility in soil.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested for persistence or biodegradability. It is expected that some biodegradation will occur to this product; however, no specific information is known.

BIO-ACCUMULATION POTENTIAL: This product has not been tested for bio-accumulation potential.

ECOTOXICITY: This product may be harmful or fatal to contaminated plant and animal-life (especially if large quantities are released). This product has not been tested for aquatic toxicity. This product may be harmful or fatal to contaminated aquatic plant and animal life.

RESULTS OF PBT AND vPvB ASSESSMENT: No data available. PBT and vPvB assessments are part of the chemical safety report required for some substances in European Union Regulation (EC) 1907/2006, Article 14.

OTHER ADVERSE EFFECTS: The components of this product are not known to have ozone depletion potential.

ENVIRONMENTAL EXPOSURE CONTROLS: Controls should be engineered to prevent release to the environment, including procedures to prevent spills, atmospheric release and release to waterways.

13. DISPOSAL CONSIDERATIONS

WASTE TREATMENT/DISPOSAL METHODS: Waste disposal must be in accordance with appropriate Federal, State, and local regulations. This product, if unaltered by use, may be disposed of by treatment at a permitted facility or as advised by your local hazardous waste regulatory authority. All gowns, gloves, and disposable materials used in the preparation or handling of this drug should be disposed of in accordance with established hazardous waste disposal procedures. Incineration is recommended. Reusable equipment should be cleaned with soap and water. It is the responsibility of the generator to determine at the time of disposal whether the product meets the criteria of a hazardous waste per regulations of the area in which the waste is generated and/or disposed of. Incineration is recommended for the product and disposable equipment. Shipment of wastes must be done with appropriately permitted and registered transporters.

DISPOSAL CONTAINERS: Waste materials must be placed in and shipped in appropriate 5-gallon or 55-gallon poly or metal waste pails or drums. Permeable cardboard containers are not appropriate and should not be used. Ensure that any required marking or labeling of the containers be done to all applicable regulations.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

U.S. EPA WASTE NUMBER: Not applicable to wastes consisting only of this product.

EUROPEAN EWC WASTE CODE: Wastes from natal care, diagnosis, treatment, or prevention of disease in humans: cytotoxic and cytostatic medicines, 18-01-08

14. TRANSPORTATION INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION: This product is NOT classified as dangerous goods, per U.S. DOT regulations, under 49 CFR 172.101.

TRANSPORT CANADA TRANSPORTATION OF DANGEROUS GOODS REGULATIONS: This product does NOT meet the criteria as Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product does NOT meet the criteria as Dangerous Goods, per rules of IATA.

EUROPEAN AGREEMENT CONCERNING THE INTERNATIONAL CARRIAGE OF DANGEROUS GOODS BY ROAD (ADR): This product does NOT meet the criteria as Dangerous Goods of the United Nations Economic Commission for Europe.

15. REGULATORY INFORMATION

ADDITIONAL U.S. REGULATIONS:

U.S. SARA REPORTING REQUIREMENTS: The components of this product are not subject to the reporting requirements of Sections 302, 304, and 313 of Title III of the Superfund Amendments and Reauthorization Act.

U.S. SARA THRESHOLD PLANNING QUANTITY: There are no specific Threshold Planning Quantities for the components of this product. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) may apply, per 40 CFR 370.20.

U.S. SARA HAZARD CATEGORIES (SECTION 311/312, 40 CFR 370-21): ACUTE: Yes; CHRONIC: Yes; FIRE: No; REACTIVE: No; SUDDEN RELEASE: No

U.S. CERCLA REPORTABLE QUANTITY (RQ): Not applicable.

U.S. TSCA INVENTORY STATUS: This product is regulated under Food and Drug Administration (FDA) standards; this product is not subject to requirements under TSCA.

OTHER U.S. FEDERAL REGULATIONS: This product is regulated under FDA regulations.

CALIFORNIA SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT (PROPOSITION 65): The components of this product are not on the California Proposition 65 lists.

ADDITIONAL CANADIAN REGULATIONS:

CANADIAN DSL/NDL STATUS: This product is regulated by the Therapeutic Products Programme (TPP) of Health Canada; it is exempt from the requirements of CEPA.

CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) PRIORITY SUBSTANCES LISTS: Components are not on the CEPA substances lists.

OTHER CANADIAN REGULATIONS: Requirements under the Canadian Health Canada, Laboratory Biosafety Guidelines may be applicable.

CANADIAN WHMIS CLASSIFICATION and SYMBOLS: The WHMIS Requirements of the Hazardous Products Act does not apply in respect of the advertising, sale or importation of any cosmetic, device, drug or food within the meaning of the Food and Drugs Act.

ADDITIONAL EUROPEAN REGULATIONS:

SAFETY, HEALTH, AND ENVIRONMENTAL REGULATIONS/LEGISLATION SPECIFIC FOR THE PRODUCT: Formulated, finished medicinal products for human use, are subject to Directive 2001/83/EC and subsequent amendments to the directive.

CHEMICAL SAFETY ASSESSMENT: No Data Available. The chemical safety assessment is required for some substances according to European Union Regulation (EC) 1907/2006, Article 14.

16. OTHER INFORMATION

ANSI LABELING (Z129.1, Provided to Summarize Occupational Hazard Information): **DANGER!** CONTAINS CYTOTOXIC AGENT. ALL EXPOSURE MUST BE MINIMIZED. ACCIDENTAL INJECTION CAN BE FATAL. MAY BE HARMFUL IF SWALLOWED, INHALED OR ON SKIN. MAY CAUSE REPRODUCTIVE EFFECTS AND MAY CAUSE HARM DURING PREGNANCY. CONTAINS SUSPECT MUTAGEN. CAN CAUSE SEVERE ADVERSE EFFECTS ON NEUROLOGICAL, NERVOUS, IMMUNE AND BLOOD FORMING SYSTEMS. MAY CAUSE RESPIRATORY SYSTEM, EYE, AND SKIN IRRITATION. This product should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Avoid accidental injection. Avoid accidental ingestion. Avoid contact with skin, eyes, and clothing. Keep container closed. Use gloves, safety glasses, and appropriate respiratory and body protection.

FIRST-AID: If swallowed, do not induce vomiting. Never give anything by mouth to an unconscious person. In case of contact, immediately flush skin with copious amounts of warm water for 20 minutes. Remove contaminated clothing and shoes. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. If ingested, do not induce vomiting. Seek medical attention. **IN CASE OF FIRE:** Use water fog, dry chemical or CO₂, or alcohol foam. **IN CASE OF SPILL:** Wipe-up spilled product with polypad or other suitable absorbent material. Decontaminate area with soapy water. Place in a suitable container. Refer to SDS for additional information.

In addition to standard pharmacy labeling practices, all syringes and IV bags containing this product should be labeled as follows:

SPECIAL HANDLING AND DISPOSAL REQUIRED

16. OTHER INFORMATION (Continued)

GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

67/548/EEC EU LABELING/CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

CLASSIFICATION FOR COMPONENTS:

FULL TEXT GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008:

FLUDARABINE PHOSPHATE: The following is a Self-Classification.

Classification: Acute Oral Toxicity Category 5, Acute Dermal Toxicity Category 5, Acute Inhalation Toxicity Category 5, Specific Target Organ Toxicity (neurological, immune, central nervous and blood forming systems by injection) Repeated Exposure Category 1, Germ Cell Mutagenicity Category 2, Reproductive Toxicity Category 2

Signal Word: Danger

Hazard Statements: H303 + H313 + H333: May be harmful if swallowed, in contact with skin or if inhaled. H341: Suspected of causing genetic effects. H351: Suspected of causing cancer. H361fd: Suspected of damaging fertility. Suspected of damaging the unborn child. H372: Causes damages to organs (neurological, central nervous, peripheral nervous, immune, bone marrow and, reproductive systems) through prolonged or repeated exposure by injection.

Hazard Symbols/Pictograms: GHS07, GHS08

ALL OTHER COMPONENTS:

An official classification for these substances has not been published in the CLP 1272: 2008.

FULL TEXT EU 67/548/EEC:

FLUDARABINE PHOSPHATE: The following is a Self-Classification.

Classification: Harmful, Reproductive Toxicity Category 3, Germ Cell Mutagenicity Category 3

Risk Phrases: R20/21/22: Harmful by inhalation, in contact with skin and if swallowed. R62/63: Possible risk of impaired fertility. Possible risk of harm to the unborn child. R68: Possible risk of irreversible effects.

Hazard Symbol: Xn

ALL OTHER COMPONENTS:

An official classification for these substances has not been published in Commission Directives 93/72/EEC, 94/69 EC, 96/54/EC or subsequent directives.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION: Bridging principles were used to classify this product.

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DEFINITIONS OF TERMS

A large number of abbreviations and acronyms appear on a SDS. Some of these, which are commonly used, include the following:

CAS #: This is the Chemical Abstract Service Number that uniquely identifies each constituent.

EXPOSURE LIMITS IN AIR:

CEILING LEVEL: The concentration that shall not be exceeded during any part of the working exposure.

ACGIH - American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits.

DFG MAK Germ Cell Mutagen Categories: 1: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed humans. 2: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed mammals. 3A: Substances which have been shown to induce genetic damage in germ cells of human or animals, or which produce mutagenic effects in somatic cells of mammals *in vivo* and have been shown to reach the germ cells in an active form. 3B: Substances which are suspected of being germ cell mutagens because of their genotoxic effects in mammalian somatic cell *in vivo*; in exceptional cases, substances for which there are no *in vivo* data, but which are clearly mutagenic *in vitro* and structurally related to known *in vivo* mutagens. 4: Not applicable (Category 4 carcinogenic substances are those with non-genotoxic mechanisms of action. By definition, germ cell mutagens are genotoxic. Therefore, a Category 4 for germ cell mutagens cannot apply. At some time in the future, it is conceivable that a Category 4 could be established for genotoxic substances with primary targets other than DNA [e.g. purely aneugenic substances] if research results make this seem sensible.) 5: Germ cell mutagens, the potency of which is considered to be so low that, provided the MAK value is observed, their contribution to genetic risk for humans is expected not to be significant.

DFG MAK Pregnancy Risk Group Classification: **Group A:** A risk of damage to the developing embryo or fetus has been unequivocally demonstrated. Exposure of pregnant women can lead to damage of the developing organism, even when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed. **Group B:** Currently available information indicates a risk of damage to the developing embryo or fetus must be considered to be probable. Damage to the developing organism cannot be excluded when pregnant women are exposed, even when MAK and BAT values are observed. **Group C:** There is no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are observed. **Group D:** Classification in one of the groups A-C is not yet possible because, although the data available may indicate a trend, they are not sufficient for final evaluation.

IDLH-Immediately Dangerous to Life and Health: This level represents a concentration from which one can escape within 30-minutes without suffering escape-preventing or permanent injury.

EXPOSURE LIMITS IN AIR (continued):

LOQ: Limit of Quantitation.

MAK: Federal Republic of Germany Maximum Concentration Values in the workplace.

NE: Not Established. When no exposure guidelines are established, an entry of NE is made for reference.

NIC: Notice of Intended Change.

NIOSH CEILING: The exposure that shall not be exceeded during any part of the workday. If instantaneous monitoring is not feasible, the ceiling shall be assumed as a 15-minute TWA exposure (unless otherwise specified) that shall not be exceeded at any time during a workday.

NIOSH RELs: NIOSH's Recommended Exposure Limits.

PEL-Permissible Exposure Limit: OSHA's Permissible Exposure Limits. This exposure value means exactly the same as a TLV, except that it is enforceable by OSHA. The OSHA Permissible Exposure Limits are based in the 1989 PELs and the June, 1993 Air Contaminants Rule (Federal Register: 58: 35338-35351 and 58: 40191). Both the current PELs and the vacated PELs are indicated. The phrase, "Vacated 1989 PEL," is placed next to the PEL that was vacated by Court Order.

SKIN: Used when there is a danger of cutaneous absorption.

STEL-Short Term Exposure Limit: Short Term Exposure Limit, usually a 15-minute time-weighted average (TWA) exposure that should not be exceeded at any time during a workday, even if the 8-hr TWA is within the TLV-TWA, PEL-TWA or REL-TWA.

TLV-Threshold Limit Value: An airborne concentration of a substance that represents conditions under which it is generally believed that nearly all workers may be repeatedly exposed without adverse effect. The duration must be considered, including the 8-hour.

TWA-Time Weighted Average: Time Weighted Average exposure concentration for a conventional 8-hr (TLV, PEL) or up to a 10-hr (REL) workday and a 40-hr workweek.

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS: This rating system was developed by the National Paint and Coating Association and has been adopted by industry to identify the degree of chemical hazards.

HEALTH HAZARD: 0 (Minimal Hazard): No significant health risk, irritation of skin or eyes not anticipated. *Skin Irritation:* Essentially non-irritating. PII or Draize = "0". *Eye Irritation:* Essentially non-irritating, or minimal effects which clear in < 24 hours [e.g. mechanical irritation]. Draize = "0". *Oral Toxicity LD₅₀ Rat:* < 5000 mg/kg. *Dermal Toxicity LD₅₀Rat or Rabbit:* < 2000 mg/kg. *Inhalation Toxicity 4-hrs LC₅₀ Rat:* < 20 mg/L.;

DEFINITIONS OF TERMS (Continued)

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS (continued):

HEALTH HAZARD (continued): 1 (Slight Hazard: Minor reversible injury may occur; slightly or mildly irritating. *Skin Irritation:* Slightly or mildly irritating. *Eye Irritation:* Slightly or mildly irritating. *Oral Toxicity LD₅₀ Rat.* > 500-5000 mg/kg. *Dermal Toxicity LD₅₀Rat or Rabbit.* > 1000-2000 mg/kg. *Inhalation Toxicity LC₅₀ 4-hrs Rat.* > 2-20 mg/L); 2 (Moderate Hazard: Temporary or transitory injury may occur. *Skin Irritation:* Moderately irritating; primary irritant; sensitizer. PII or Draize > 0, < 5. *Eye Irritation:* Moderately to severely irritating and/or corrosive; reversible corneal opacity; corneal involvement or irritation clearing in 8-21 days. Draize > 0, ≤ 25. *Oral Toxicity LD₅₀ Rat.* > 50-500 mg/kg. *Dermal Toxicity LD₅₀Rat or Rabbit.* > 200-1000 mg/kg. *Inhalation Toxicity LC₅₀ 4-hrs Rat.* > 0.5-2 mg/L); 3 (Serious Hazard: Major injury likely unless prompt action is taken and medical treatment is given; high level of toxicity; corrosive. *Skin Irritation:* Severely irritating and/or corrosive; may destroy dermal tissue, cause skin burns, dermal necrosis. PII or Draize > 5-8 with destruction of tissue. *Eye Irritation:* Corrosive, irreversible destruction of ocular tissue; corneal involvement or irritation persisting for more than 21 days. Draize > 80 with effects irreversible in 21 days. *Oral Toxicity LD₅₀ Rat.* > 1-50 mg/kg. *Dermal Toxicity LD₅₀Rat or Rabbit.* > 20-200 mg/kg. *Inhalation Toxicity LC₅₀ 4-hrs Rat.* > 0.05-0.5 mg/L); 4 (Severe Hazard: Life-threatening; major or permanent damage may result from single or repeated exposure. *Skin Irritation:* Not appropriate. Do not rate as a "4", based on skin irritation alone. *Eye Irritation:* Not appropriate. Do not rate as a "4", based on eye irritation alone. *Oral Toxicity LD₅₀ Rat.* ≤ 1 mg/kg. *Dermal Toxicity LD₅₀Rat or Rabbit.* ≤ 20 mg/kg. *Inhalation Toxicity LC₅₀ 4-hrs Rat.* ≤ 0.05 mg/L).

FLAMMABILITY HAZARD: 0 (Minimal Hazard-Materials that will not burn in air when exposure to a temperature of 815.5°C [1500°F] for a period of 5 minutes.); 1 (Slight Hazard-Materials that must be pre-heated before ignition can occur. Material require considerable pre-heating, under all ambient temperature conditions before ignition and combustion can occur, including: Materials that will burn in air when exposed to a temperature of 815.5°C (1500°F) for a period of 5 minutes or less; Liquids, solids and semisolids having a flash point at or above 93.3°C [200°F] (e.g. OSHA Class IIB, or; Most ordinary combustible materials [e.g. wood, paper, etc.]); 2 (Moderate Hazard-Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur. Materials in this degree would not, under normal conditions, form hazardous atmospheres in air, but under high ambient temperatures or moderate heating may release vapor in sufficient quantities to produce hazardous atmospheres in air, including: Liquids having a flash-point at or above 37.8°C [100°F]; Solid materials in the form of course dusts that may burn rapidly but that generally do not form explosive atmospheres; Solid materials in a fibrous or shredded form that may burn rapidly and create flash fire hazards (e.g. cotton, sisal, hemp; Solids and semisolids that readily give off flammable vapors.); 3 (Serious Hazard- Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures, or, unaffected by ambient temperature, are readily ignited under almost all conditions, including: Liquids having a flash point below 22.8°C [73°F] and having a boiling point at or above 38°C [100°F] and below 37.8°C [100°F] [e.g. OSHA Class IB and IC]; Materials that on account of their physical form or environmental conditions can form explosive mixtures with air and are readily dispersed in air [e.g., dusts of combustible solids, mists or droplets of flammable liquids]; Materials that burn extremely rapidly, usually by reason of self-contained oxygen [e.g. dry nitrocellulose and many organic peroxides]); 4 (Severe Hazard-Materials that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air, and which will burn readily, including: Flammable gases; Flammable cryogenic materials; Any liquid or gaseous material that is liquid while under pressure and has a flash point below 22.8°C [73°F] and a boiling point below 37.8°C [100°F] [e.g. OSHA Class IA; Material that ignite spontaneously when exposed to air at a temperature of 54.4°C [130°F] or below [e.g. pyrophoric]).

PHYSICAL HAZARD: 0 (*Water Reactivity:* Materials that do not react with water. *Organic Peroxides:* Materials that are normally stable, even under fire conditions and will not react with water. *Explosives:* Substances that are Non-Explosive. *Unstable Compressed Gases:* No Rating. *Pyrophorics:* No Rating. *Oxidizers:* No "0" rating allowed. *Unstable Reactives:* Substances that will not polymerize, decompose, condense or self-react.); 1 (*Water Reactivity:* Materials that change or decompose upon exposure to moisture. *Organic Peroxides:* Materials that are normally stable, but can become unstable at high temperatures and pressures. These materials may react with water, but will not release energy. *Explosives:* Division 1.5 & 1.6 substances that are very insensitive explosives or that do not have a mass explosion hazard. *Compressed Gases:* Pressure below OSHA definition. *Pyrophorics:* No Rating. *Oxidizers:* Packaging Group III; *Solids:* any material that in either concentration tested, exhibits a mean burning time less than or equal to the mean burning time of a 3:7 potassium bromate/cellulose mixture and the criteria for Packing Group I and II are not met. *Liquids:* any material that exhibits a mean pressure rise time less than or equal to the pressure rise time of a 1:1 nitric acid (65%)/cellulose mixture and the criteria for Packing Group I and II are not met. *Unstable Reactives:* Substances that may decompose, condense or self-react, but only under conditions of high temperature and/or pressure and have little or no potential to cause significant heat generation or explosive hazard. Substances that readily undergo hazardous polymerization in the absence of inhibitors.); 2 (*Water Reactivity:* Materials that may react violently with water. *Organic Peroxides:* Materials that, in themselves, are normally unstable and will readily undergo violent chemical change, but will not detonate. These materials may also react violently with water. *Explosives:* Division 1.4 – Explosive substances where the explosive effect are largely confined to the package and no projection of fragments of appreciable size or range are expected. An external fire must not cause virtually instantaneous explosion of almost the entire contents of the package. *Compressed Gases:* Pressurized and meet OSHA definition but < 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics:* No Rating. *Oxidizers:* Packaging Group II *Solids:* any material that, either in concentration tested, exhibits a mean burning time of less than or equal to the mean burning time of a 2:3 potassium bromate/cellulose mixture and the criteria for Packing Group I are not met. *Liquids:* any material that exhibits a mean pressure rise time less than or equal to the pressure rise of a 1:1 aqueous sodium chlorate solution (40%)/cellulose mixture and the criteria for Packing Group I are not met. *Unstable Reactives:* Substances that may polymerize, decompose, condense, or self-react at ambient temperature and/or pressure, but have a low potential for significant heat generation or explosion. Substances that readily form peroxides upon exposure to air or oxygen at room temperature); 3 (*Water Reactivity:* Materials that may form explosive reactions with water. *Organic Peroxides:* Materials that are capable of detonation or explosive reaction, but require a strong initiating source, or must be heated under confinement before initiation; or materials that react explosively with water.

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS (continued):

PHYSICAL HAZARD (continued): 3 (continued): *Explosives:* Division 1.2 – Explosive substances that have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but do not have a mass explosion hazard. *Compressed Gases:* Pressure ≥ 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics:* No Rating. *Oxidizers:* Packaging Group I *Solids:* any material that, in either concentration tested, exhibits a mean burning time less than the mean burning time of a 3:2 potassium bromate/cellulose mixture. *Liquids:* Any material that spontaneously ignites when mixed with cellulose in a 1:1 ratio, or which exhibits a mean pressure rise time less than the pressure rise time of a 1:1 perchloric acid (50%)/cellulose mixture. *Unstable Reactives:* Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a moderate potential to cause significant heat generation or explosion.) 4 (*Water Reactivity:* Materials that react explosively with water without requiring heat or confinement. *Organic Peroxides:* Materials that are readily capable of detonation or explosive decomposition at normal temperature and pressures. *Explosives:* Division 1.1 & 1.2-explosive substances that have a mass explosion hazard or have a projection hazard. A mass explosion is one that affects almost the entire load instantaneously. *Compressed Gases:* No Rating. *Pyrophorics:* Add to the definition of Flammability "4". *Oxidizers:* No "4" rating. *Unstable Reactives:* Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a high potential to cause significant heat generation or explosion.)

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS:

HEALTH HAZARD: 0 (materials that, under emergency conditions, would offer no hazard beyond that of ordinary combustible materials); Gases and vapors whose LC₅₀ for acute inhalation toxicity is greater than 10,000 ppm. Dusts and mists whose LC₅₀ for acute inhalation toxicity is greater than 200 mg/L. Materials whose LD₅₀ for acute dermal toxicity is greater than 2000 mg/kg. Materials whose LD₅₀ for acute oral toxicity is greater than 2000 mg/kg. Materials that are essentially non-irritating to the respiratory tract, eyes and skin. 1 (materials that, under emergency conditions, can cause significant irritation): Gases and vapors whose LC₅₀ for acute inhalation toxicity is greater than 5,000 ppm but less than or equal to 10,000 ppm. Dusts and mists whose LC₅₀ for acute inhalation toxicity is greater than 10 mg/L but less than or equal to 200 mg/L. Materials whose LD₅₀ for acute dermal toxicity is greater than 1000 mg/kg but less than or equal to 2000 mg/kg. Materials whose LD₅₀ for acute oral toxicity is greater than 500 mg/kg but less than or equal to 2000 mg/kg. Materials that cause slight to moderate irritation to the respiratory tract, eyes and skin. 2 (materials that, under emergency conditions, can cause temporary incapacitation or residual injury): Gases and vapors whose LC₅₀ for acute inhalation toxicity is greater than 3,000 ppm but less than or equal to 5,000 ppm. Dusts and mists whose LC₅₀ for acute inhalation toxicity is greater than 2 mg/L but less than or equal to 10 mg/L. Materials whose LD₅₀ for acute dermal toxicity is greater than 200 mg/kg but less than or equal to 1000 mg/kg. Materials whose LD₅₀ for acute oral toxicity is greater than 50 mg/kg but less than or equal to 500 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC₅₀ for acute inhalation toxicity, if its LC₅₀ is less than or equal to 5000 ppm and that does not meet the criteria for either degree of hazard 3 or degree of hazard 4. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause severe tissue damage, depending on duration of exposure. Materials that are respiratory irritants. Materials that cause severe, but reversible irritation to the eyes or are lachrymators. Materials that are primary skin irritants or sensitizers. 3 (materials that, under emergency conditions, can cause serious or permanent injury): Gases and vapors whose LC₅₀ for acute inhalation toxicity is greater than 1,000 ppm but less than or equal to 3,000 ppm. Dusts and mists whose LC₅₀ for acute inhalation toxicity is greater than 0.5 mg/L but less than or equal to 2 mg/L. Materials whose LD₅₀ for acute dermal toxicity is greater than 40 mg/kg but less than or equal to 200 mg/kg. Materials whose LD₅₀ for acute oral toxicity is greater than 5 mg/kg but less than or equal to 50 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC₅₀ for acute inhalation toxicity, if its LC₅₀ is less than or equal to 3000 ppm and that does not meet the criteria for degree of hazard 4. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause frostbite and irreversible tissue damage. Materials that are respiratory irritants. Cryogenic gases that cause frostbite and irreversible tissue damage. Materials that are corrosive to the respiratory tract. Materials that are corrosive to the eyes or cause irreversible corneal opacity. Materials that are corrosive to the skin. 4 (materials that, under emergency conditions, can be lethal): Gases and vapors whose LC₅₀ for acute inhalation toxicity less than or equal to 1,000 ppm. Dusts and mists whose LC₅₀ for acute inhalation toxicity is less than or equal to 0.5 mg/L. Materials whose LD₅₀ for acute dermal toxicity is less than or equal to 40 mg/kg. Materials whose LD₅₀ for acute oral toxicity is less than or equal to 5 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC₅₀ for acute inhalation toxicity, if its LC₅₀ is less than or equal to 1000 ppm.

FLAMMABILITY HAZARD: 0 Materials that will not burn under typical fire conditions, including intrinsically noncombustible materials such as concrete, stone, and sand; Materials that will not burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in accordance with Annex D. 1 Materials that must be preheated before ignition can occur. Materials in this degree require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur. Materials that will burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in accordance with Annex D. Liquids, solids and semisolids having a flash point at or above 93.4°C (200°F) (i.e. Class IIB liquids). Liquids with a flash point greater than 35°C (95°F) that do not sustain combustion when tested using the *Method of Testing for Sustained Combustibility*, per 49 CFR 173, Appendix H or the *UN Recommendation on the Transport of Dangerous Goods, Model Regulations* (current edition) and the related *Manual of Tests and Criteria* (current edition). Liquids with a flash point greater than 35°C (95°F) in a water-miscible solution or dispersion with a water non-combustible liquid/solid content of more than 85 percent by weight. Liquids that have no fire point when tested by ASTM D 92 Standard Test Method for Flash and Fire Points by Cleveland Open Cup, up to a boiling point of the liquid or up to a temperature at which the sample being tested shows an obvious physical change. Combustible pellets with a representative diameter of greater than 2 mm (10 mesh). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed up flash point of the solvent. Most ordinary combustible materials. 2 Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur.

DEFINITIONS OF TERMS (Continued)

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

FLAMMABILITY HAZARD (continued): 2 (continued): Materials in this degree would not under normal conditions form hazardous atmospheres with air, but under high ambient temperatures or under moderate heating could release vapor in sufficient quantities to produce hazardous atmospheres with air: Liquids having a flash point at or above 37.8°C (100°F) and below 93.4°C (200°F) (i.e. Class II and Class IIIA liquids.) Solid materials in the form of powders or coarse dusts of representative diameter between 420 microns (40 mesh) and 2 mm (10 mesh) that burn rapidly but that generally do not form explosive mixtures in air. Solid materials in fibrous or shredded form that burn rapidly and create flash fire hazards, such as cotton, sisal and hemp. Solids and semisolids that readily give off flammable vapors. Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent. **3** Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures or, though unaffected by ambient temperatures, are readily ignited under almost all conditions: Liquids having a flash point below 22.8°C (73°F) and having a boiling point at or above 37.8°C (100°F) and those liquids having a flash point at or above 22.8°C (73°F) and below 37.8°C (73°F) and below 37.8°C (100°F) (i.e. Class IB and IC liquids). Materials that, on account of their physical form or environmental conditions, can form explosive mixtures with air and are readily dispersed in air. Flammable or combustible dusts with a representative diameter less than 420 microns (40 mesh). Materials that burn with extreme rapidity, usually by reason of self-contained oxygen (e.g. dry nitrocellulose and many organic peroxides). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent. **4** Materials that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air and will burn readily: Flammable gases. Flammable cryogenic materials. Any liquid or gaseous materials that is liquid while under pressure and has a flash point below 22.8°C (73°F) and a boiling point below 37.8°C (100°F) (i.e. Class IA liquids). Materials that ignite when exposed to air, Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent.

INSTABILITY HAZARD: 0 Materials that in themselves are normally stable, even under fire conditions: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) below 0.01 W/mL. Materials that do not exhibit an exotherm at temperatures less than or equal to 500°C (932°F) when tested by differential scanning calorimetry. **1** Materials that in themselves are normally stable, but that can become unstable at elevated temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 0.01 W/mL and below 10 W/mL. **2** Materials that readily undergo violent chemical change at elevated temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 10 W/mL and below 100W/mL. **3** Materials that in themselves are capable of detonation or explosive decomposition or explosive reaction, but that require a strong initiating source or that must be heated under confinement before initiation: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 100 W/mL and below 1000 W/mL. Materials that are sensitive to thermal or mechanical shock at elevated temperatures and pressures. **4** Materials that in themselves are readily capable of detonation or explosive decomposition or explosive reaction at normal temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) of 1000 W/mL or greater. Materials that are sensitive to localized thermal or mechanical shock at normal temperatures and pressures.

FLAMMABILITY LIMITS IN AIR:

Much of the information related to fire and explosion is derived from the National Fire Protection Association (NFPA). **Flash Point** - Minimum temperature at which a liquid gives off sufficient vapors to form an ignitable mixture with air. **Autoignition Temperature**: The minimum temperature required to initiate combustion in air with no other source of ignition. **LEL** - the lowest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source. **UEL** - the highest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source.

TOXICOLOGICAL INFORMATION:

Human and Animal Toxicology: Possible health hazards as derived from human data, animal studies, or from the results of studies with similar compounds are presented. Definitions of some terms used in this section are: **LD₅₀** - Lethal Dose (solids & liquids) which kills 50% of the exposed animals; **LC₅₀** - Lethal Concentration (gases) which kills 50% of the exposed animals; **ppm** concentration expressed in parts of material per million parts of air or water; **mg/m³** concentration expressed in weight of substance per volume of air; **mg/kg** quantity of material, by weight, administered to a test subject, based on their body weight in kg. Other measures of toxicity include **TDLo**, the lowest dose to cause a symptom and **TCLo** the lowest concentration to cause a symptom; **TDo**, **LDLo**, and **LDo**, or **TC**, **TCo**, **LCLo**, and **LCo**, the lowest dose (or concentration) to cause lethal or toxic effects. **Cancer Information:** The sources are: **IARC** - the International Agency for Research on Cancer; **NTP** - the National Toxicology Program, **RTECS** - the Registry of Toxic Effects of Chemical Substances, **OSHA** and **CAL/OSHA**. IARC and NTP rate chemicals on a scale of decreasing potential to cause human cancer with rankings from 1 to 4. Subrankings (2A, 2B, etc.) are also used. **Other Information:** **BEI** - ACGIH Biological Exposure Indices, represent the levels of determinants which are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the TLV.

REPRODUCTIVE TOXICITY INFORMATION:

A **mutagen** is a chemical which causes permanent changes to genetic material (DNA) such that the changes will propagate through generational lines. An **embryotoxin** is a chemical which causes damage to a developing embryo (i.e. within the first eight weeks of pregnancy in humans), but the damage does not propagate across generational lines. A **teratogen** is a chemical which causes damage to a developing fetus, but the damage does not propagate across generational lines. A **reproductive toxin** is any substance which interferes in any way with the reproductive process.

ECOLOGICAL INFORMATION:

EC is the effect concentration in water. **BCF** = Bioconcentration Factor, which is used to determine if a substance will concentrate in lifeforms which consume contaminated plant or animal matter. **TL_m** = median threshold limit; Coefficient of Oil/Water Distribution is represented by **log K_{ow}** or **log K_{oc}** and is used to assess a substance's behavior in the environment.

REGULATORY INFORMATION:

U.S. and CANADA:

ACGIH: American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits.

This section explains the impact of various laws and regulations on the material. **EPA** is the U.S. Environmental Protection Agency. **NIOSH** is the National Institute of Occupational Safety and Health, which is the research arm of the U.S. Occupational Safety and Health Administration (**OSHA**). **WHMIS** is the Canadian Workplace Hazardous Materials Information System. **DOT** and **TC** are the U.S. Department of Transportation and the Transport Canada, respectively. Superfund Amendments and Reauthorization Act (**SARA**); the Canadian Domestic/Non-Domestic Substances List (**DSL/NDL**); the U.S. Toxic Substance Control Act (**TSCA**); Marine Pollutant status according to the **DOT**; the Comprehensive Environmental Response, Compensation, and Liability Act (**CERCLA** or **Superfund**); and various state regulations. This section also includes information on the precautionary warnings which appear on the material's package label. **OSHA** - U.S. Occupational Safety and Health Administration.

EUROPEAN and INTERNATIONAL:

The DFG: This is the Federal Republic of Germany's Occupation Health Agency, similar to the U.S. OSHA. **EU** is the European Community (formerly known as the **EEC**, European Economic Community). **EINECS:** This is the European Inventory of Now-Existing Chemical Substances. The **ARD** is the European Agreement Concerning the International Carriage of Dangerous Goods by Road and the **RID** are the International Regulations Concerning the Carriage of Dangerous Goods by Rail. **AICS** is the Australian Inventory of Chemical Substances. **MITI** is the Japanese Minister of International Trade and Industry.